CROSSTALK

CrossTalk proposal: Rotors have been demonstrated to drive human atrial fibrillation

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Introduction

It is our pleasure to debate this important and clinically relevant topic. Atrial fibrillation (AF) is a leading cause of hospitalization and death (Calkins *et al.* 2012), and the need to improve AF therapy is urgent and requires dramatic advances in our mechanistic understanding. Decades of research have not dented the incidence of AF, now at epidemic proportions (Calkins *et al.* 2012), nor reduced its morbidity and mortality with the laudable exception of antithrombotic therapy (Calkins *et al.* 2012).

Our position

AF is initiated by triggers from regions including the pulmonary veins (Calkins *et al.* 2012), then sustained by specific mechanisms. We will present substantial evidence that these sustaining mechanisms include localized rotors in many patients.

Our position that 'rotors have been demonstrated to drive [human] AF' summarizes a century of bench-to-bedside studies, culminating in recent multicentre clinical trials in which ablation of AF rotors has eliminated AF and improved patient outcomes. Conversely, there is a paucity of evidence supporting the opposing notion: that disorganized activity *per se* sustains AF without underlying driving mechanisms.

Many studies that propose disorganized mechanisms are limited to 'long-standing persistent AF'. Conversely, we provide evidence for a comprehensive mechanistic framework in which rotors sustain AF across clinical 'classes'. The terms paroxysmal AF (self-limiting), persistent and longstanding persistent AF (continuous for >7 days and >1 year, respectively) are highly dependent on how often ECGs are obtained, since AF is often asymptomatic (Charitos *et al.* 2012) and patients with persistent AF may spontaneously present in sinus rhythm (Calkins *et al.* 2012) and could thus be reclassified as paroxysmal AF (Jahangir *et al.* 2007).

Definitions

While AF appears disorganized on the ECG, the atria clearly exhibit regions of spatio-temporal organization and disorganization. The debate on whether disorganization in AF is *caused* ('driven') by sources (Pandit & Jalife, 2013) or whether disorganization *per se* sustains AF (Fig. 1) has been ongoing for a century (Jalife, 2011).

Spatially localized sources can be divided into rotors and focal sources. We define a 'rotor' as the phase singularity whose reverberations radiate 'spiral waves' at high speed into surrounding tissue (Pandit & Jalife, 2013). The spatial domain of 1:1 activation by a rotor depends on its frequency relative to the heterogeneity of local refractory periods. In the context of cardiac arrhythmias, rotors are highly localized drivers or organizing sources of reentrant tachycardia and fibrillation (Pandit & Jalife, 2013). Although not our primary topic, a focal source is an ectopic site from where activation spreads centrifugally based on regional refractoriness and conduction (Pandit & Jalife, 2013). Rotors have long been demonstrated in animal models of AF (Pandit & Jalife, 2013), and more recently in human AF where brief targeted ablation alone can terminate AF (Narayan *et al.* 2013*b*) and eliminate AF long term (Narayan *et al.* 2013*a*).

Conversely, it has been posited that AF depends on the disorganization of wavelets, itself due to longitudinal/transmural dissociation (de Groot *et al.* 2010). However, this is supported by mapping <10–20% of MRI-quantified atrial areas (Jadidi *et al.* 2013) in small numbers of patients without proof of causality (de Groot *et al.* 2010).

Evidence for our position

Many diverse observations are readily explained and in fact predicted by our position, yet unexplained by disorganization alone (Fig. 1). Human AF resistant even to electrical cardioversion can be terminated by very few or even a single (Herweg *et al.* 2003) ablation lesion(s) (Calkins *et al.* 2012; Narayan *et al.* 2012*b*), or by localized physical pressure (Tzou *et al.* 2011). Propagation vectors in AF repeat reproducibly over time (Gerstenfeld *et al.* 1992) and exhibit consistent spatio-temporal features (Sahadevan *et al.* 2004; Sanders *et al.* 2005; Atienza *et al.* 2009). These observations

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are difficult to reconcile with disorganized sustaining mechanisms, yet support spatially localized AF-sustaining regions in these patients.

Direct evidence for localized AF-sustaining mechanisms, including rotors, has been established in a variety of experimental systems. Optical mapping that utilizes voltage-sensitive dyes and contemporary signal-processing algorithms (Gray *et al.* 1998) has demonstrated AF rotors producing spatial gradients in the distribution of dominant atrial frequencies, the highest frequency lying at the rotor location (Fig. 1; Mansour *et al.* 2001). Clinical interventions show that ablation of high dominant frequency sites that eliminates left-to-right atrial frequency gradients predicts long-term freedom from AF (Atienza *et al.* 2009).

Direct clinical evidence for rotors now exists in patients with paroxysmal, persistent and longstanding persistent AF. Since human AF is spatially non-uniform, we used bi-atrial basket catheters (Narayan *et al.* 2013*b*) to *simultaneously* map much larger areas than in previous studies (de Groot *et al.* 2010) and then applied phase analysis to detect regions that activate sequentially but may be obscured by the fibrillatory milieu. Simultaneous analysis of wide areas increases the sensitivity to detect rotors that precess (show limited meander), and is essential to prove or disprove their existence. Yet, to the best of our knowledge, simultaneous analysis of wide areas is absent in studies supporting disorganized mechanisms (de Groot *et al.* 2010; Lee *et al.* 2014). Although higher spatial resolution would be welcome, we reasoned from minimum bi-atrial (Narayan *et al.* 2012*a*) repolarization (~110 ms) and conduction velocity (~40 cm s^{-1}) that human atria can support 1:1 conduction from a rotor in circuit paths as short as ~4–5 cm (Rensma *et al.* 1988). Clinical electrode spacing can map such reentry (Rappel & Narayan, 2013).

The CONFIRM trial (CONventional ablation for AF with or without Focal Impulse and Rotor Modulation, FIRM) used this approach in 92 patients at 107 procedures to reveal rotors (or focal sources) in 97% of patients with paroxysmal, persistent and longstanding persistent AF. Rotors were concurrent (2.1 ± 1.0 per patient), more prevalent with advanced AF (Narayan *et al.* 2012*b*), and precessed in ~2–3 cm^2 areas (Narayan *et al.* 2013*b*) causing irregular electrograms at the rotor tip (Zlochiver *et al.* 2008) and varying spiral waves from fibrillatory disorganization. Notably, causality was proven by the ability of brief targeted ablation to eliminate AF acutely and on long-term follow-up, with (Narayan *et al.* 2012*b*) or without (Narayan *et al.* 2013*a*) other ablation. These results are now independently validated (Shivkumar *et al.* 2012; Miller *et al.* 2013), and laboratories worldwide have identified rotors in human AF using diverse methods, including phase mapping (Ghoraani *et al.* 2013; Haissaguerre *et al.* 2013; Lin *et al.* 2013; Lee *et al.* 2014). Studies are defining how localized ablation eliminates AF, possibly analogous to the proven elimination of micro-reentrant atrial tachycardia by focal ablation.

Limitations of the opposing position

While it is often assumed that Maze surgery supports disorganized mechanisms (Moe *et al.* 1964), the numbers of lesions (Cox *et al.* 1991) are insufficient to constrain dozens or hundreds of the wavelets proposed (de Groot *et al.* 2010). Since rotors need 'elbow room' (typically 2× the centre of rotation or ~5–10 mm), Maze may in fact simply prevent rotors from sustaining. Indeed, one original motivation for Maze was to intersect relatively large reentrant drivers (Cox *et al.* 1991).

Notably, studies supporting AF disorganization involved few patients (n = 49) (de Groot *et al.* 2010), and mapped only 10–21 cm^2 or <10–20% of MRI-defined left atrial areas (100–138 cm^2) (Jadidi *et al.* 2013). It is unclear why this work (de Groot *et al.* 2010) consistently fails to show any rotational activity in human AF, since others now show rotations of varying duration depending on the size of the mapping plaque and technique (Ghoraani *et al.* 2013; Haissaguerre *et al.* 2013; Lin *et al.* 2013; Narayan *et al.* 2013*b*; Lee *et al.* 2014). It is possible that activation mapping of these difficult-to-interpret AF electrograms (Fig. 1; de Groot *et al.* 2010) obscures rotation evident in other approaches (e.g. phase mapping). Importantly, to the best of our knowledge, interventions have never been used to prove that disorganization is an AF-sustaining mechanism rather than just a bystander to another mechanism (e.g. rotors). Finally, the disorganized AF hypothesis is inconsistent with and cannot easily explain the wealth of clinical and experimental data supporting localized AF sources in at least some patients as discussed above.

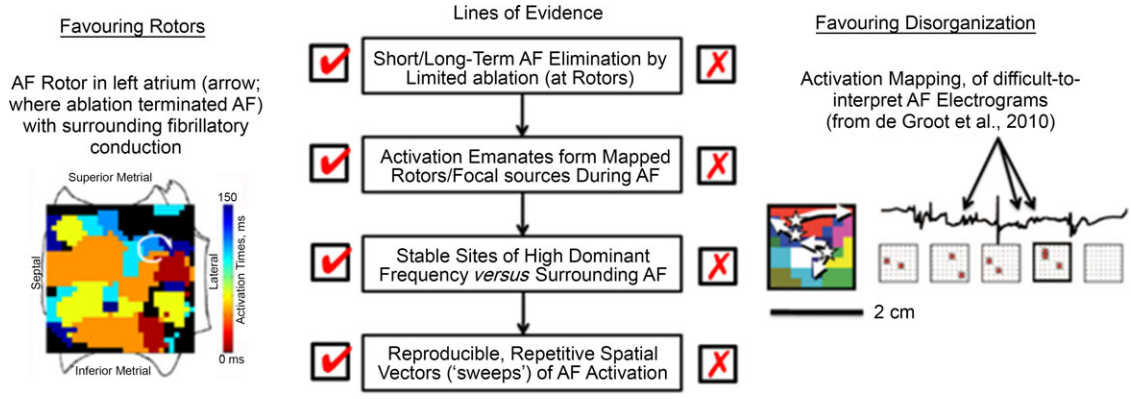

Figure 1. Lines of evidence favouring rotors over disorganized mechanisms for AF
Left human rotor (where ablation terminated AF) surrounded by fibrillatory conduction. Right, disorganized AF maps, but created from analysis of difficult-to-interpret AF electrograms (de Groot *et al.* 2010).

Conclusions and future directions

Rotors have been proven to sustain AF in patients in all clinical subtypes and numerous animal models. These data come from various groups using diverse methods with interventions and long-term outcomes to prove causality. The opposing contention, that rotors do not exist but that AF is sustained by disorganization without driving sources, is supported only circumstantially by experiments with important technical limitations, in a small numbers of patients, and with no proof of causality. Mapping and therapy of AF rotors has already substantially improved clinical outcomes in multicentre trials. Future work should define how electrical, structural or neural remodelling contributes to the formation of AF sources and disorganization from them to remaining tissue.

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Additional information

Competing interests

S. M. Narayan is co-author of intellectual property owned by the University of California Regents and licensed to Topera Inc. (San Diego, CA, USA). Topera does not sponsor any research, including that presented here. S. M. Narayan holds equity in Topera, and reports having received honoraria from Medtronic, St Jude Medical and Biotronik. J. Jalife serves on the Scientific Advisory Board of Topera, Inc.

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